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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,521	12/05/2003	Atul Varadhachary	HO-P02703US2	8270

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EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/728,521	VARADHACHARY ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-10,14-20,26-32 and 38-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-10,14-20,26-32 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1, 7-10, 14-20, 26-32 and 38-40 are pending.

Applicants' amendment filed February 13, 2006 is acknowledged. Applicant's response has been fully considered. Claims 1, 8-10, 15, 16, 26-27, 31, 32 and 38 have been amended. Therefore, claims 1, 7-10, 14-20, 26-32 and 38-40 are examined.

Withdrawn Claim Rejections - 35 USC § 112

2. The previous rejection of claims 8-10, 15 and 16 under 35 U. S. C. 112, second paragraph as being indefinite, is withdrawn in view of applicant's amendment to the claim, and applicants' response at page 6 in the amendment filed February 13, 2006.

Withdrawn Claim Rejections - 35 USC § 103

3. The previous rejection of claims 8, 9, 10, 15 and 16 under 35 U. S. C. 103(a) as being unpatentable over by Van Bree *et al.* (WO 01/72322, October 4, 2001), is withdrawn in view of applicant's amendment to the claim in the amendment filed February 13, 2006.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 7-10, 14-20, 26-32 and 38-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating bacteremia, sepsis, enhancing a mucosal immune response in the gastrointestinal in a subject, decreasing mortality of a subject having bacteremia or sepsis, comprising administering orally to the subject an

effective amount of a lactoferrin composition comprising at least 1% to 50% of an N-terminal lactoferrin variant, wherein the variant has a deletion and/or substitution of 1 to 16 N-terminal amino acid residues of lactoferrin and retains the same biological function as the full length of lactoferrin (see paragraphs [0046] and [0063]); or a method of treating bacterial infection using a pharmaceutical composition comprising an N-terminal lactoferrin variant as indicated in the prior art, does not reasonably provide enablement for a method of treating bacteremia, sepsis, enhancing a mucosal immune response in the gastrointestinal in a subject, decreasing mortality of a subject having bacteremia or sepsis, comprising administering orally to the subject an effective amount of a lactoferrin composition comprising at least 1% to 50% of an N-terminal lactoferrin variant having a deletion and/or substitution of 1 to 16 N-terminal amino acid residues of lactoferrin, where the function of the N-terminal lactoferrin variant is not defined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1, 7-10, 14-20, 26-32 and 38-40 are directed to a method of treating bacteremia, sepsis, enhancing a mucosal immune response in the gastrointestinal in a subject, decreasing mortality of a subject having bacteremia or sepsis, comprising administering orally to the subject an effective amount of a lactoferrin composition comprising at least 1% to 50% of an N-terminal lactoferrin variant having a deletion and/or substitution of 1 to 16 N-terminal amino acid residues of lactoferrin. The specification, however, only discloses cursory conclusions without data supporting the findings, which states that the instant invention is directed to a method for treating bacteremia, sepsis, septic shock or related conditions, the method comprising oral administration

of a lactoferrin composition, which comprises lactoferrin or an N-terminal lactoferrin variant in which at least the N-terminal glycine residue is truncated or substituted, or lactoferrin lacking one or more N-terminal residues or having one or more substitutions in the N-terminal (page 4, paragraphs [0011] and [0012]). There are no indicia that the present application enables the full scope in view of the method of treating bacteremia, sepsis, septic shock or related conditions using a lactoferrin composition comprising an N-terminal lactoferrin variant as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the absence or presence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the N-terminal lactoferrin variants having a deletion and/or substitution of 1 to 16 N-terminal amino acid residues of lactoferrin, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

Examples 3-6 indicate the use and effect of rhLF in the murine LPS model of sepsis and bacteremia; Example 16 indicates using rhLF in the reduction of mortality and key cytokines in sepsis; and Example 17 indicates anti-sepsis effect of three different rhLF preparations

containing different percentage of N-1 truncates. However, there are no other working examples indicating the effects of various N-terminal lactoferrin variants in the treatment.

(3). The state of the prior art and relative skill of those in the art:

The prior art (e.g., Van Bree *et al.*, WO 01/72322) teach human lactoferrin (hLF) or LF variants (e.g., N-terminal variants), which have the biological activities of natural LF, can be used to treat large scale (bacterial) infection or blood-borne infection (sepsis); and Nuijens et al. (USPN 6,333,311) teach lactoferrin variants with one or more arginine residues in the N-terminal region deleted are used for treating inflammation. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identification of functional N-terminal lactoferrin variants and their effects in the treatment to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method for treating bacteremia, sepsis or related conditions, comprising administering orally to the subject an effective amount of a lactoferrin composition comprising at least 1% to 50% of an N-terminal lactoferrin variant having a deletion and/or substitution of 1 to 16 N-terminal amino acid residues of lactoferrin. Although the specification indicates the use of specific N-terminal lactoferrin variant (e.g., N-1 truncate) in treating sepsis, the specification has not identified functional N-terminal lactoferrin variants in the treatment, the invention is highly unpredictable regarding the structures of functional N-terminal lactoferrin variants and their effects in the treatment.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method for treating bacteremia, sepsis or related conditions, comprising administering orally to the subject an effective amount of a lactoferrin composition comprising at least 1% to 50% of an N-terminal lactoferrin variant having a deletion and/or substitution of 1 to 16 N-terminal amino acid residues of lactoferrin. The specification indicates the use and effect of rhLF in the murine LPS model of sepsis and bacteremia (Examples 3-6), the use of rhLF in the reduction of mortality and key cytokines in sepsis (Example 16), and anti-sepsis effect of three different rhLF preparations containing different percentage of N-1 truncates (Example 17). However, the specification has not shown the correlation of the structure and function for the N-terminal variants. Since the specification does not provide sufficient teachings on the correlation of structure and function for N-terminal variants, it is necessary to carry out undue experimentation to identify functional N-terminal variant of lactoferrin and to assess its effect in treating bacteremia, sepsis or related conditions.

(6). Nature of the Invention

The scope of the claims encompass a method for treating bacteremia, sepsis or related conditions, comprising administering orally to the subject an effective amount of a lactoferrin composition comprising at least 1% to 50% of an N-terminal lactoferrin variant having a deletion and/or substitution of 1 to 16 N-terminal amino acid residues of lactoferrin, however, the specification does not provide sufficient teachings on the identification of a functional N-terminal lactoferrin variant, nor demonstrates the effect of the variant in treating bacteremia, sepsis or related conditions. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed methods associated with variants, the structure of a functional N-

terminal variant is unpredictable, and the teachings in the specification are limited, therefore, it is necessary to carry out undue experimentation to identify the functional variants and to assess their effects in the treatment.

Response to Arguments

Applicants indicate claims have been amended to recite N-terminal lactoferrin variant has a deletion, substitution or combination thereof of 1 to 16 N-terminal amino acid residues. In view of these amendments, the rejection should be withdrawn.

Applicants' response has been fully considered, however, the argument is not found persuasive because the specification has not shown the correlation between the structure and function of N-terminal variants, where the functional N-terminal variant cannot be readily identified without further experimentation, thus the effects of the N-terminal variants having a deletion, substitution or combination thereof of 1 to 16 N-terminal amino acid residues in the treatment is not predictable. Therefore, the full scope of the claims is not enabled.

Maintained Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Previous rejection of claims 1, 7, 14, 17-19, 26-32 and 38-40 under 35 U.S.C. 103(a) as being unpatentable over by Van Bree *et al.* (WO 01/72322, October 4, 2001) is maintained, and the response to argument is shown below.

Van Bree *et al.* teach human lactoferrin (hLF) can block free LPS and cause them to clear from the body more rapidly, and mask their inflammatory activity; and hLF or LF variants (e.g., N-terminal variants with 1-4 arginine deleted, hLF-2N, hLF-3N, hLF-4N, hLF-5N; pages 4, 5 and 27), which have the biological activities of natural LF, can be used to treat large scale (bacterial) infection, blood-borne infection (sepsis) as well as inflammation resulting from an infection (pages 3-4; page 20, lines 24-29; page 24; claim 1), where the concentration of the polypeptide (LF or LF variant) in the pharmaceutical composition can be at least 1% to 20% by weight (page 24, lines 10-12); and lactoferrin/variant can be administered orally in the form of a solid or solution, and the active components can be encapsulated in gelatin capsules together with inactive ingredients and carriers such as glucose, mannitol or magnesium carbonate (an antacid; claim 14), and the formulated solid or liquid formulations can be in an enteric-coated form (page 26; claims 7, 17-19). Although the reference does not provide a specific example for a method of treating bacteremia, enhancing a mucosal immune response or decreasing mortality using a lactoferrin composition containing the N-terminal variant, it indicates a high dose of hLF or LF variant (e.g., N-terminal variant) having the biological activity of natural LF can be orally administered in the treatment, and hLF or LF variants can be used in treating large scale (bacterial) infection, blood-borne infection (sepsis) as well as inflammation resulting from an infection (see above), which has the same method step as the claimed invention, thus at the time of invention was made, it would have been obvious to one of ordinary skill in the art to orally

administer N-terminal variant of LF in the method of treating bacteremia, enhancing a mucosal immune response or decreasing mortality to produce the desired effect as the LF (claims 26-32, 38-40), which results in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

Response to Arguments

Applicant indicates to establish a prima facie case for obviousness, all claim limitations must be found or suggested in the references cited or within the general knowledge in the art. Van Bree neither discloses nor suggests the N-terminal lactoferrin variants of the pending claims (See pg. 10 - pg. 11, line 3). Van Bree et al. does not disclose or suggest lactoferrin compositions comprising at least 1% to at least 50% w/w of an N-terminal lactoferrin variants. In addition to finding a disclosure or suggestion of all claim limitations, a prima facie case for obviousness requires an established motivation to combine, or, as in this case, to modify a prior art reference. The Examiner's attempts to offer a rationale for modifying Van Bree. In essence, the reasoning is that the method steps coincide with those in Van Bree (See Examiner's Office Action Dated 12/5/05, pg. 9, lines 5-14). This amount to an argument that the reference could be modified to the claimed methods, this alone is legally insufficient to establish a prima facie case for obviousness (pages 7-8 of the response).

Applicants' response has been considered, however, the argument is not found persuasive because of the following reasons. Van Bree *et al.* disclose the N-terminal lactoferrin variants can be lactoferrin having 1-4 arginine residues from the first cluster (i.e., residues 2-5) deleted (see e.g., page 4, lines 13-14; page 5, lines 6-28; page 11, lines 6-11). Van Bree *et al.* also indicate

the concentration of the polypeptide (LF or LF variant) in the pharmaceutical composition is at least 1% to 20% by weight (page 24, lines 10-12; page 25, lines 22-24). Furthermore, the reference teaches hLF or LF variants can be used to treat large scale (bacterial) infection, blood-borne infection (sepsis) as well as inflammation resulting from an infection (pages 3-4; page 20, lines 24-29; page 24). Since the reference teaches orally administering the same lactoferrin peptide to patients to treat bacterial infection or sepsis, which would inherently produce the desired effect (e.g., enhancing a mucosal immune response, decreasing mortality, or reducing the levels of circulating cytokines) as the claimed invention, and which was, as a whole, prima facie obvious at the time the claimed invention was made.

Conclusion

6. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
April 20, 2006